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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/291,347	04/14/1999	JULIAN ALEXIS JOHN HANAK	CACO-0051	1979

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EXAMINER	
RAMIREZ, DELIA M	
ART UNIT	**PAPER NUMBER**
1652	

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18

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/291,347	HANAK ET AL.	
	Examiner	Art Unit	
	Delia M. Ramirez	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 April 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-18 and 37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-18 and 37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *4/14/1999* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Application

Claims 4-18 and 37 are pending.

It is noted that the examination of the instant application has been assigned to a different Examiner in Group Art Unit 1652.

Applicant's amendment of claims 4-9, 11, addition of claim 37, and cancellation of claims 1-3 and 36 in Paper No. 17, filed on 4/4/2002 is acknowledged.

Applicant's amendments and/or cancellation of claims 1-3 and 36 presented in Paper No. 17, filed on 4/4/2002 are deemed sufficient to overcome some of the rejections previously applied in Paper No. 16, mailed on 11/28/2001. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Specification

1. The use of the trademarks has been noted in this application. See, for example, "Pharmacia" or "Hellma". It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Drawings

2. The drawings have been reviewed and are objected under 37 CFR 1.84 or 1.152. See attached Notice of Draftsperson's Patent Drawing Review. Applicant is required to submit the drawing corrections within the time period set in the attached Office communication. See 37 CFR 1.85(a). Failure to take corrective action within the set period will result in ABANDOMENT of the application. In addition, if amendments to the specification are needed due to drawing corrections, Applicant is requested to submit such amendments while the case is being prosecuted to expedite processing of the application.

Claim Objections

3. Claim 18 is objected to because of the following informalities: for clarity, the term "said RNase being" should be replaced with "wherein said RNase is". Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 4-18 and 37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5. Claims 4 and 37 (claims 5-18 dependent thereon) are indefinite in the recitation of "RNase in an amount sufficient to degrade substantially all of the RNA" as the term "substantially" is a relative term not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is suggested that Applicants quantify the level of degradation intended, if support for such quantification is present in the specification. Correction is required.

6. Claim 4 (claims 5-18 dependent thereon) is indefinite in the recitation of "incubating said lysate" as it is unclear from the claims as written which cell lysates are being incubated. Claim 4 requires two cell lysates, however, the incubation step refers to one lysate. This is confusing because, from Applicant's disclosure, the cellular component has to be exposed to the RNase, which can only happen if both lysates are incubated. Correction is required. For examination purposes, the term "incubating said lysate" will be interpreted as "incubating said lysates" when appropriate.

7. Claim 7 is indefinite in the recitation of "recombinant carbohydrate" as it is unclear what the meaning of the term "recombinant carbohydrate" is. Correction is required.

8. Claims 11-15 (claims 16-18 dependent thereon) are indefinite in the recitation of "regulated manner" as it is unclear and confusing absent a statement indicating what is being regulated. Biosynthesis of cellular elements is intrinsically regulated therefore one cannot determine how the claims are being further limited. It is suggested that if Applicant's intended regulation is that of the expression of the gene encoding the RNase, the term "regulated manner"

be deleted. Correction is required. For examination purposes, the term "regulated manner" has not been given patentable weight as its meaning is unclear.

9. Claims 9 and 18 are indefinite in the recitation of "non-specific RNase" as it is unclear and confusing. It is not clear if the term "non-specific" refers to any RNase or if it refers to a genus of RNases which lack specificity to an unknown element. It is suggested that Applicant's clearly indicate the element to which the lack of specificity is directed to. Correction is required. For examination purposes, the term "non-specific" has been given no patentable weight as its meaning is undefined.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 4-18 and 37 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 4 and 37 (claims 5-18 dependent thereon) are directed to a genus of methods for the preparation of RNA-free cellular components, wherein any cell producing any RNase can be used. The specification discloses the use of *E. coli* to express DNA encoding RNase I and RNaseA (pages 47-64). The specification also discloses *E. coli* capable of expressing a cellular component such as plasmid DNA or recombinant proteins, wherein said *E. coli* has been

transformed to express and secrete RNaseI and RNaseA to the periplasm using inducible or constitutive promoters. The use of *S. typhimurium, Bacillus, Streptomyces*, and *Pseudomonas* is discussed (pages 13-15). However, no disclosure of other host cells or RNases, as encompassed by the claims, has been provided. While the prior art discloses the DNA structure of a few RNases, many RNases are not disclosed by the specification or the prior art. In addition, since the claimed method encompasses the use of any cell, some knowledge or guidance as to which promoters can be used in different hosts is required to practice the claimed method. The specification describe a few of the elements required to practice the claimed genus of methods, which is insufficient to put one of skill in the art in possession of the attributes and features of the claimed method. Thus, one of skill in the art cannot reasonably conclude that Applicant had possession of the claimed invention at the time the instant application was filed.

11. Claims 4-18 and 37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for preparing RNA-free cellular components in an *E. coli* cell, wherein the cellular component and RNaseI or RNaseA are produced by said *E. coli* cell and wherein RNaseI or RNaseA are expressed and secreted using an inducible or constitutive promoter, does not reasonably provide enablement for a method for preparing RNA-free cellular components wherein any RNase is expressed in any cell and wherein any RNase is expressed constitutively in the cytoplasm. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The criteria for undue experimentation, summarized in *re Wands*, 8, USPQ2nd 1400 (Fed. Cir. 1988) are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented, 3) the presence and absence of working examples, 4) the nature of the invention, 5) the state of prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breath of the claims.

The scope of claims 4-18 and 37 is so broad as to encompass a method for preparing RNA-free cellular components expressing any RNase in any host cell. As explained previously, the specification discloses the use of *E. coli* to express DNA encoding RNase I and RNaseA (pages 47-64). The specification also discloses *E. coli* capable of expressing cellular components such as plasmid DNA or recombinant proteins, wherein said *E. coli* has been transformed to express and secrete RNaseI and RNaseA to the periplasm using inducible or constitutive promoters. The use of *S. typhimurium, Bacillus, Streptomyces*, and *Pseudomonas* is discussed (pages 13-15). However, no disclosure of other host cells or RNases, as encompassed by the claims, has been provided. No working examples of other host cells or RNases as claimed have been provided. While one could argue that the prior art discloses the structure of other RNases and that cloning of the DNA encoding such RNases in several host cells is considered routine in the art, the scope of the claims encompasses RNases and host cells not disclosed by the specification or the prior art. Therefore, some knowledge or guidance as to DNA structures encoding RNases and which promoters can be used in different host cells is required to practice the claimed method.

Claims 4-14, 18 and 37 as written encompass a method for preparing RNA-free cellular components wherein the RNase is expressed in the cytoplasm (without a secretion signal). It is

not clear how one can practice the claimed method if the RNases are expressed constitutively in the cytoplasm since RNases are known in the art as enzymes which would degrade RNA molecules, therefore expression of foreign RNases or expression of RNases at higher than normal levels can result in the degradation of essential RNA in the cytoplasm which can affect cell growth and survival. See the teachings of Okorokov et al. (Protein Expression and Purification 6:472-480, 1995; Abstract; cited in the specification). Therefore, due to the lack of relevant examples, the amount of information provided, the lack of knowledge about DNA structures encoding RNases, promoters, and cells as previously discussed, and the unpredictability of the art in regard to constitutive expression of RNases in the cytoplasm, one of ordinary skill in the art would have to go through the burden of undue experimentation in order to isolate DNA encoding RNases, isolate and/or test promoters in different host cells to express said RNases, or determine if the claimed method can be practiced with constitutive expression of said RNases without secretion of said RNases. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to use the invention in a manner reasonably correlated with the scope of the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 4, 6-7, 9-13, and 15-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over McMaster et al. (Analytical Biochemistry 109:47-54, 1980; cited in the IDS) in view of Okorokov et al. (Protein Expression and Purification 6:472-480, 1995; cited in the specification). McMaster et al teaches the production and purification of plasmid DNA in *E. coli* by culturing *E. coli*, isolating the *E. coli* cells, lysing said cells, and adding RNaseA to the lysate to eliminate RNA contaminants (page 49, columns 1 and 2; Large scale preparations of plasmid DNA). McMaster et al does not teach using unpurified RNaseA from a cell lysate. Okorokov et al. teaches the expression of bovine RNaseA in *E. coli* by transforming said cell with a plasmid containing DNA encoding said RNaseA linked to the phoA signal peptide under the control of the P_R and T7/trc promoters. Okorokov et al. also teaches the isolation of the RNaseA by osmotic shock to obtain a cell lysate containing said RNaseA (page 473, column 2, Isolation of the periplasmic proteins). Okorokov et al. does not teach the production of plasmid DNA.

Claim 4, 6, 9-11 are directed to a method of preparing RNA-free cellular components wherein the cellular component and RNase are produced in different cells and wherein said cells are lysed and the lysates are combined and incubated to allow RNase to digest RNA molecules.

Claim 7 requires that the cellular component is selected from the group consisting of recombinant DNA, recombinant protein, and recombinant carbohydrate. Claims 12-13 and 15-18 are directed to the same method with the following additional limitations (1) the RNase is overproduced, (2) the RNase is inducibly produced, or (3) the RNase is secreted out of the cytoplasm.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the cell lysate comprising the plasmid DNA, as taught by McMaster et al., and the cell lysate containing RNaseA, as taught by Okorokov et al., to obtain RNA-free plasmid DNA. A person of ordinary skill in the art is motivated to use the RNaseA-containing preparation in the plasmid DNA preparation because RNaseA is widely used in the inactivation of RNA molecules. One of ordinary skill in the art has a reasonable expectation of success at combining the plasmid DNA-containing lysate and the RNaseA-containing lysate to inactivate RNA molecules, since McMaster et al. teaches the use of RNaseA to inactivate RNA in the plasmid DNA-containing preparation. Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made.

14. Claims 8 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over McMaster et al. (Analytical Biochemistry 109:47-54, 1980; cited in the IDS) in view of Okorokov et al. (Protein Expression and Purification 6:472-480, 1995; cited in the specification) as applied to claims 4 and 11 and further in view of Zhu et al. (J. Bacteriol. 172:3146-3151, 1990). The teachings of McMaster et al. and Okorokov et al. have been discussed above. Zhu et al. teaches *E. coli* strains wherein the DNA encoding RNaseI has been inserted into the *E. coli*

chromosome and RNaseI is produced constitutively (page 3147, Results, columns 1 and 2). Zhu et al. also teaches cell lysates comprising said RNase (page 3147, Table 1). Neither McMaster et al. nor Okorokov et al. teach constitutive expression of RNaseA for secretion to the periplasm or RNaseA encoded by a gene that is integrated into the genome of *E. coli*. Zhu does not teach large-scale production of plasmid DNA nor does it teach RNaseA fused to a signal peptide.

Claims 8 and 14 are directed to the method of claim 4 as discussed above with the additional limitation that the gene encoding the RNase be inserted into the chromosome of the host cell or the RNase be constitutively produced.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to insert the DNA coding for the RNaseA linked to a signal peptide, as taught by Okorokov et al, into the chromosome and express the RNase constitutively, as taught by Zhu, in the method of McMaster et al. in view of Okorokov et al. A person of ordinary skill in the art is motivated to (1) express the RNase constitutively because constitutive expression does not require an inducer and (2) insert the DNA encoding the RNase into the chromosome of the host cell in order to create a mutant strain capable of expressing said RNase or to avoid the instability associated with plasmids. One of ordinary skill in the art has a reasonable expectation of success at practicing the method as claimed because Zhu et al. teaches the constitutive expression of RNaseI in *E. coli* by insertion of DNA encoding RNaseI in the chromosome of *E. coli*. Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made.

Conclusion

15. No claim is in condition for allowance.

16. Applicants are requested to submit a clean copy of the pending claims (including amendments, if any) in future written communications to aid in the examination of this application.

17. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 308-4556. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (703) 306-0288. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (703) 308-3804. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

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